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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/759,878	01/16/2004	Samuel Jotham Reich	129402.00701	1285

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EXAMINER	
GIBBS, TERRA C	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 08/25/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/759,878	REICH ET AL.	
	Examiner	Art Unit	
	Terra C. Gibbs	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 August 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-77* is/are pending in the application.

4a) Of the above claim(s) *1-31* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *32-77* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *16 January 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *10/25/04 & 3/22/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This Office Action is a response to Applicant's Amendment and Election filed August 14, 2006.

Claims 1-77 are pending in the instant application. Claims 32, 34, 35, 60, 65, and 75 have been amended.

Claims 1-31 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on August 14, 2006.

Election/Restrictions

Applicant's election with traverse of Group III (claims 32-77) in the reply filed on August 14, 2006 is acknowledged. The traversal is on the ground(s) that the search classification for each invention Group will substantially overlap. Applicants argue that the claims are directed to isolated siRNA, wherein the sense strand comprises a nucleotide sequence identical to a target sequence in human or mouse ICAM-1 mRNA and methods of using the isolated siRNAs. Applicants contend that the Examiner will not be seriously burdened by searching and considering the inventions as described in all the currently pending claims.

Applicant's arguments and contentions have been fully considered but are not found persuasive because first, the search classification for Groups I and II is not the

same as that recited for Group III, and thus the search classification would not overlap. For example, Groups I and II have the same search classification, however, Group III has an entirely different search classification than that of Groups I and II. For this reason alone, it is apparent that the search classification for each invention Group will not substantially overlap, and would therefore constitute a serious search burden on the Examiner to examine all the distinct Groups in one application.

Second, although the search classification (e.g. class 536, subclass 24.5) for an isolated siRNA, wherein the sense strand comprises a nucleotide sequence identical to a target sequence in human or mouse ICAM-1 mRNA would substantially overlap, a sequence search for isolated siRNA targeted **human** ICAM-1 mRNA (Group I) or isolated siRNA targeted **mouse** ICAM-1 (Group 2) would not overlap since the two are distinct and independent sequences, very different from each other. In this regard, a sequence search of one Group would not reveal art against the other distinct and independent Group.

In summary, the Restriction Requirement mailed July 12, 2006 was a restriction of distinct and independent inventions: unique and structurally distinct nucleotide sequences. A search of isolated siRNA targeted **human** ICAM-1 mRNA would not encompass all the art relevant to isolated siRNA targeted **mouse** ICAM-1 mRNA and therefore the inventions are not coextensive. Since the search for isolated siRNA targeted **human** ICAM-1 mRNA is not entirely coextensive with a search for isolated siRNA targeted **mouse** ICAM-1 mRNA, it would be burdensome to search the inventions of these Groups together in one application.

Therefore, the requirement is still deemed proper and is therefore made FINAL.

Claims 32-77 have been examined on the merits.

Priority

Applicant's reference to priority in the first sentence of the specification is acknowledged. It is noted that the instant specification claims priority to U.S. Provisional Application 60/440,579, filed January 16, 2003.

Information Disclosure Statement

Applicant's information disclosure statements filed October 25, 2004 and March 22, 2006 are acknowledged. The submissions are in compliance with the provisions of 37 CFR §1.97. Accordingly, the Examiner has considered the information disclosure statements and signed copies are enclosed herewith.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 32-77 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter

which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

The subject matter of the instantly claimed invention is drawn to methods of administering an isolated siRNA to a subject comprising administering a sense RNA stand and an antisense RNA strand targeted to human ICAM-1, such that human ICAM-1 mRNA is degraded.

The specification teaches a series human ICAM-1 target sequences for siRNAs tested in HEK-293 cells (see the instant specification at Table 2, hICAM #1-10). It is noted that the sequence for which these target sequences originate from is human ICAM-1 represented by SEQ ID NO:1 in the instant invention. A brief review of the prior art teaches human ICAM-1 mRNA with different GenBank Accession Numbers. For example, the prior art teaches GenBank Accession Numbers: X06990 and J03132. However, neither the instant specification, nor the prior art describe isolated siRNA targeted to human ICAM-1, other than the above sequences listed.

At the outset, it is noted that the rejected claims do not recite any sequence identifier relating to human ICAM-1. This sequence is thus considered to be defined by its function (i.e. the activity of human ICAM-1) rather than by any one specific structure. Accordingly, the claims embrace siRNA targeted to human ICAM-1, or any such molecule with analogous human ICAM-1 activity, known or yet to be discovered, along with any isoform or allele present within this species, or any variant, polymorphic or otherwise, that is within reasonable similarity from these families of proteins that retain

human ICAM-1 activity.

To satisfy the written-description requirement, the specification must describe every element of the claimed invention in sufficient detail so that one of ordinary skill in the art would recognize that the inventor possessed the claimed invention at the time of filing. Thus, an applicant complies with the written-description requirement by describing the invention, with all its claimed limitations, and by using such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention. To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical, structure/function correlation, methods of making the claimed product, and any combination thereof. The representative sample requirement may be satisfied by supplying structural or functional information, or a combination of both, such that one of skill in the art would be satisfied that applicants were in possession of the genus as claimed. Further, the size of the representative sample required is an inverse function of the unpredictability of the art.

See the January 5, 2001 (Vol. 66, No. 4, pages 1099-1111) Federal Register for the Guidelines for Examination of Patent Applications Under the 35 USC 112 ¶ 1, "Written Description" Requirement. These guidelines state: "[T]o satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. An applicant shows possession of the claimed

invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. Possession may be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was "ready for patenting" such as by the disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that applicant was in possession of the claimed invention.

Further, See MPEP § 2163, which states "[A] biomolecule sequence described only by a functional characteristic, without any known or disclosed correlation between that function and the structure of the sequence, normally is not a sufficient identifying characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence."

In order to synthesize the isolated siRNA targeted to human ICAM-1 and to practice the methods claimed, one of skill would first need the sequence of the human ICAM-1. Although the instant specification teaches a series of target sequences for human ICAM-1, the claims embrace siRNAs directed to *any* sequence of *any* human ICAM-1, or any such molecule with analogous human ICAM-1 activity, known or yet to be discovered, along with any isoform or allele present within this species, or any variant, polymorphic or otherwise, that is within reasonable similarity from these families of proteins that retain human ICAM-1 activity. Apart from further experimentation, the skilled artisan would not have been able to predict the structures of the full scope of the

claimed siRNA molecules encompassed by the instant invention, particularly in the absence of any teaching by way of structure or reference to active domains or regions. The genus is not immediately envisioned because the genus of isolated siRNA targeted to human ICAM-1 is considered to include not only the human ICAM-1 sequences taught in the instant invention and the prior art, but also any such molecule with analogous human ICAM-1 activity, known or yet to be discovered. However, the distinguishing characteristics of the claimed genus are not considered to be described herein, or in the prior art. Thus, because one of skill in the art could not envision any siRNA targeted to human ICAM-1, other than those described in the instant specification, one of skill would not be convinced that Applicants were in possession of any isolated siRNA targeted to human ICAM-1 sequences that are heretofore undescribed.

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The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 32-77 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. This is an enablement rejection.

The following factors have been considered in formulating this rejection (*In re Wands*, 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988)): the breadth of the claims, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, the amount of direction or guidance presented, the presence or absence of working examples of the invention, and the quantity of experimentation necessary.

The above invention is drawn to methods of administering an isolated siRNA to a subject comprising administering a sense RNA stand and an antisense RNA strand targeted to human ICAM-1, such that human ICAM-1 mRNA is degraded. The above invention is also drawn to methods of administering an isolated siRNA to a subject comprising administering a sense RNA stand and an antisense RNA strand targeted to human ICAM-1, such that a pathology or disease is inhibited or treated. It is noted that the instant specification at page 22, lines 10 and 11 discloses, "As used herein, a "subject" includes a human being or non-human animal. Preferably, the subject is a human being". The broadness of the methods recited in the instant claims explicitly implies *in vivo* applicability for enablement purposes.

The specification discloses the inhibition of human ICAM-1 expression in HEK 293 cells in culture using siRNAs targeted to human ICAM-1 (see Figure 2). The instant specification also teaches the cytotoxicity profile of HEK cells, *in vitro*, following the administration of siRNAs targeted to human ICAM-1 (see Figure 3).

The specification teaches prophetic methods of administering an isolated siRNA targeted to human ICAM-1 to a subject. For example, the instant specification at

Examples 2-5 teaches, "[I]ntravitreal injections of siRNA targeted to ICAM-1 **will be** performed"... "[N]on-specific siRNA **will be** injected as a control"... "**[I]t is expected that** intravitreal injection of siRNA targeted to ICASM-1 will decrease permeability and leukostasis"... "**[I]t is expected that** siRNA targeted to ICAM-1 applied to the cornea after limbal injury will decrease the resultant area of neovascularization of the cornea in mice"... and "**[I]t is expected that** intravitreal injection of siRNA targeted to ICAM-1 will decrease the area of laser-induced CNV in mice". The specification provides only for methods of using isolated siRNA to inhibit the expression of human ICAM-1 in cultured cells *in vitro*.

The specification does not demonstrate any correlation with a method of inhibiting human ICAM-1 expression in cells in culture (*in vitro*) with methods of administering an isolated siRNA targeted to human ICAM-1 to a subject. The specification does not present any examples wherein an isolated siRNA targeted to human ICAM-1 was delivered to cells in a subject (*in vivo*) and gene expression is inhibited. Nor does the specification provide any examples wherein an isolated siRNA targeted to human ICAM-1 was delivered to cells *in vivo* and a therapeutic benefit is resultant or a disease is treated.

The specification as filed does not provide sufficient guidance or appropriate examples that would enable a skilled artisan to use the claimed methods in *in vivo* environments. Additionally, a person skilled in the art would recognize that predicting the efficacy of a compound, particularly an siRNA compound, *in vivo,* based solely on its performance *in vitro* is unpredictable. Thus, although the specification discloses

general methodologies of using siRNA compounds *in vivo*, such a disclosure would not be considered enabling since the state of the art of siRNA-mediated gene inhibition in living organisms is highly unpredictable. The factors listed below have been considered in the analysis of enablement:

(A) The breadth of the claims;
(B) The nature of the invention;
(C) The state of the prior art;
(D) The level of one of ordinary skill;
(E) The level of predictability in the art;
(F) The amount of direction provided by the inventor;
(G) The existence of working examples; and
(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The following references are cited herein to illustrate the state of the art of delivery of siRNAs into targeted cells, tissues, and organs *in vivo*:

Lu et al. (2005) in *RNA Interference Technology* (Cambridge, Appasani, ed.), page 303, state that "Unlike *in vitro* transfection of siRNA into cells, *in vivo* delivery of siRNA into targeted tissue in animal models is much more complicated, involving physical, chemical and biological approaches, and in some cases their combination." Therapeutic applications, however, clearly depend upon optimized local and systemic delivery of siRNA *in vivo*. "....limited reports of *in vivo* studies have indicated a lack of effective delivery methods for siRNA agents." "...the two most critical hurdles are maintaining its [siRNA] stability *in vivo* and delivery to disease tissues and cells."

Samarsky et al. in *RNA Interference Technology,* (Cambridge, Appasani, ed.), (2005) pages 389-394, appear to agree with Lu et al., stating that "Delivery of RNAi to target cells and tissues in mammalian organism[s] is considerably more difficult than in

cultured cells. This step is likely to be a critical bottleneck in the *in vivo* application of RNAi." "One major remaining obstacle is the efficient delivery of RNAi triggers to target tissues *in vivo.*" (page 394).

Downward, J. (BMJ, 2004 Vol. 328:1245-1428) outlines that RNAi can be used as an effective therapeutic strategy, however considerable problems relating to delivery to target cells will have to be solved (see Abstract). Downward further addresses the unpredictability and the problems faced in the siRNA art with the following statements: "Although a big improvement on previous methods, RNA interference has its limitations. Not every sequence works - most researchers get a success rate of about one in three. In addition, although the effects are generally thought to be highly sequence specific, some question marks remain as to whether or not some of the effects seen are "off target"" (see page 1246, last paragraph). Downward adds, "RNA interference clearly has much promise in the laboratory"... "However a huge gap exists between achieving results *in vitro* and in a whole animal or patient" (see page 1247, second column, first paragraph). Downward concludes with, "The major challenge in turning RNA interference into an effective therapeutic strategy is the delivery of the RNA interference agents... to the target cells within the body" (see page 1247, second column).

Paroo et al. (Trends in Biotechnology, 2004 Vol. 22:390-394) address the unpredictability associated with siRNA therapy with the following statements: "In contrast to the great success of synthetic siRNA in mammalian cell culture, there have been few reports employing synthetic siRNA in animals. Developing siRNA for efficient gene silencing *in vivo* is likely to be more challenging and many issues must be

addressed before use in animals can become routine". Paroo et al. also state, "Crucial pharmacological and chemical challenges will need to be addressed before siRNA can fulfill its immense promise" (see page 393, last paragraph).

Fjose et al. (Birth Defects Research, 2006 Vol. 78:150-171) teach that, "[R]apid advances have been made in the development of RNA-based technologies and promising results have been obtained from studies on mammalian cell culture systems and animal *in vivo* models. However, the progress in our understanding of the RNAi pathway and the related function of miRNAs have also raised concerns regarding various types of side effects that may restrict the use of this technology in human therapy" (see Abstract). Fjose et al. also teach, "[P]reviously, extensive research on the development of therapeutic antisense nucleic acids has revealed problems regarding delivery, stability, off-target effects, and target sequence selection; these problems will also challenge the therapeutic potential of RNAi" (see page 165, first paragraph)... and "[T]he problem of delivery is still considered to be the major obstacle to the clinical use of RNAi-based therapy" (see page 165, second column).

A review of the instant application fails to find adequate guidance or any disclosure exemplifying the *in vivo* applications as broadly claimed. Although, Applicants clearly recognize the potential of siRNA molecules for reducing human ICAM-1 mRNA expression *in vivo,* Applicants do not teach the ordinary artisan how to effectively deliver siRNA molecules to target tissues and cells *in vivo* to reduce human ICAM-1 gene expression, more-or-less treat a disease. A review of the instant application finds working examples directed to the inhibition of human ICAM-1

expression and cytotoxicity profiles in HEK 293 (*in vitro*) following the administration of siRNAs targeted to human ICAM-1. No technical guidance or exemplary disclosure is provided regarding the therapeutic use of the claimed methods for targeting and inhibiting human ICAM-1 in living organisms, including any mammal, using siRNA. As the references above indicate, cell culture results are not readily extrapolated to *in vivo* applications.

Thus, it is maintained that the prior art at the time of Applicant's filing would not enable the use of siRNA *in vitro* to support claims directed to the *in vivo* use of siRNA, let alone claims directed to delivering siRNA *in vivo* for the treatment of a disease. Accordingly, one skilled in the art, being unable to use the prior art for such guidance, must necessarily find such guidance from the specification. However, one of skill would not find the guidance provided in the specification in the form of *in vitro* examples enough to overcome the unpredictability and challenges of applying results from *in vitro* experiments to the *in vivo* methods of inhibition, as exemplified in the references above.

In order to practice the invention using the specification and the state of the prior art as outlined above, the quantity of experimentation required to practice the invention as claimed *in vivo* would require the *de novo* determination of those siRNA that are successfully delivered to target sites in appropriate cells and/or tissues such that human ICAM-1 gene expression is degraded or a disease is treated in a whole organism. Since the specification fails to provide any real guidance for methods of using siRNA *in vivo*, and since resolution of the various complications in regards to targeting a particular gene in a living organism is unpredictable, one of skill in the art would have

been unable to practice the invention without engaging in undue trial and error experimentation.

Conclusion

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Terra C. Gibbs whose telephone number is 571-272-0758. The examiner can normally be reached on 9 am - 5 pm M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on 571-272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

tcg
August 18, 2006